



Louisiana

Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Policy # 00272

Original Effective Date: 10/20/2010

Current Effective Date: 04/01/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Microarray-based Gene Expression Analysis for Prostate Cancer Management is addressed separately in medical policy 00403.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the following genetic and protein biomarkers for the diagnosis of prostate cancer to be **investigational***:

- Kallikrein markers (eg, 4Kscore^{™†} Test)
- *TMPRSS: ERG* fusion genes
- Candidate gene panels
- Mitochondrial DNA variant testing (eg, Prostate Core Mitomics Test^{™†})
- Gene hypermethylation testing (eg, ConfirmMDx^{®†})
- Prostate Health Index (phi).
- *HOXC6* and *DLX1* testing (eg, SelectMDx)
- PCA3, ERG, and SPDEF RNA expression in exosomes (eg, ExoDx Prostate IntelliScore)
- *PCA3* testing (eg, ProgenSA PCA3 Assay)
- Autoantibodies ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, and CSNK2A2 (eg, Apifyny)

Based on review of available data, the Company considers single nucleotide variant testing for cancer risk assessment of prostate cancer to be **investigational.***

Policy Guidelines

GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUMAN Genome Organization, and by the Human Genome Variation Society itself.

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The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview PROSTATE CANCER

Prostate cancer is the second most common cancer in men, with a predicted 161,360 incidence cases and 26,730 deaths expected in the United States in 2017.

Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. Early localized disease can usually be treated with surgery and radiotherapy, although active surveillance may be adopted

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in men whose cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In patients with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. The lifetime risk of being diagnosed with prostate cancer for men in the United States is approximately 16%, while the risk of dying of prostate cancer is 3%. African American men have the highest prostate cancer risk in the United States; the incidence of prostate cancer is about 60% higher and the mortality rate is more than 2 to 3 times greater than that of white men. Autopsy results have suggested that about 30% of men age 55 and 60% of men age 80 who die of other causes have incidental prostate cancer, indicating that many cases of cancer are unlikely to pose a threat during a man's life expectancy.

Grading

The most widely used grading scheme for prostate cancer is the Gleason system. It is an architectural grading system ranging from 1 (well differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization. A cross-walk of these grading systems is shown in Table 1.

Table 1. Prostate Cancer Grading Systems

Grade Group	Gleason Score (Primary and Secondary Pattern)	Cells
1	6 or less	Well differentiated (low grade)
2	7 (3 + 4)	Moderately differentiated (moderate grade)
3	7 (4 + 3)	Poorly differentiated (high grade)
4	8	Undifferentiated (high grade)
5	9-10	Undifferentiated (high grade)

Numerous genetic alterations associated with development or progression of prostate cancer have been described, with the potential for the use of these molecular markers to improve the selection process of men who should undergo prostate biopsy or rebiopsy after an initial negative biopsy.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. The following laboratories are certified under the Clinical Laboratory Improvement Amendments: BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore[®])[†], ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test[™])[†], MDx Health (SelectMDx, ConfirMDx), Innovative Diagnostics (phi[™])[†], and ExoDx[®] Prostate (Exosome

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Diagnostics). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In February 2012, the Progenas[®] PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progenas PCA3 Assay (Hologic Gen-Probe) has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had one or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on current standard of care. The Progenas PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter) was approved by the FDA through the premarket approval process. The phi test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Genetic and protein biomarker tests are best evaluated within the framework of a diagnostic or prognostic test because such frameworks provide diagnostic and prognostic information that assists in clinical management decisions. Because these tests are used as an adjunct to the usual diagnostic workup, it is important to evaluate whether the tests provide incremental information above the standard workup to determine whether the tests have utility in clinical practice.

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BIOMARKER TESTING FOR SELECTION OF MEN FOR INITIAL PROSTATE BIOPSY

Clinical Context and Test Purpose

The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of men who should undergo initial biopsy. Conventional decision-making tools for identifying men for prostate biopsy include digital rectal exam (DRE), serum prostate-specific antigen (PSA), and patient risk factors such as age, race, and family history of prostate cancer.

DRE has relatively low interrater agreement among urologists, with estimated sensitivity, specificity, and positive predictive value (PPV) for diagnosis of prostate cancer of 59%, 94%, and 28%, respectively. DRE might have a higher PPV in the setting of elevated PSA.

The risk of prostate cancer increases with increasing PSA levels; an estimated 15% of men with a PSA level of 4 ng/mL or less and normal DRE, 30% to 35% of men with a PSA level between 4 ng/mL and 10 ng/mL, and more than 67% of men with a PSA level greater than 10 ng/mL will have biopsy-detectable prostate cancer. Use of PSA levels in screening has improved detection of prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial and Göteborg Randomised Prostate Cancer Screening Trial trials demonstrated that biennial PSA screening reduces the risk of being diagnosed with metastatic prostate cancer.

However, elevated PSA levels are not specific to prostate cancer; levels can be elevated due to infection, inflammation, trauma, or ejaculation. In addition, there are no clear cutoffs for cancer positivity with PSA. Using a common PSA level cutoff of 4.0 ng/mL, the American Cancer Society (2010) systematically reviewed the literature and calculated pooled estimates of elevated PSA sensitivity of 21% for detecting any prostate cancer and 5% for detecting high-grade cancers with an estimated specificity of 91%.

Existing screening tools have led to unnecessary prostate biopsies. More than 1 million prostate biopsies are performed annually in the United States, with a resulting cancer diagnosis in 20% to 30% of men. About one-third of men who undergo prostate biopsy experience transient pain, fever, bleeding, and urinary difficulties. Serious biopsy risks (eg, bleeding or infection requiring hospitalization) have estimated rates ranging from less than 1% to 3%.

Given the risk, discomfort, burden of biopsy, and low diagnostic yield, there is a need for noninvasive tests that distinguish potentially aggressive tumors that should be referred for biopsy from clinically insignificant localized tumors or other prostatic conditions that do not need biopsy with the goal of avoiding low-yield biopsy.

The question addressed in this evidence review is: Does the use of testing for genetic protein biomarkers improve the net health outcome in men being considered for an initial prostate biopsy?

The following PICOTS were used to select literature to inform this review.

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Patients

The relevant population is men for whom an initial prostate biopsy is being considered because of clinical symptoms (eg, difficulty with urination, elevated PSA).

The population for which these tests could be most informative is men in the indeterminate or “gray zone” range of PSA level on repeat testing with unsuspecting DRE findings. Repeat PSA testing is important because results initially reported being between 4 ng/mL and 10 ng/mL frequently revert to normal. The gray zone for PSA levels is usually between 3 or 4 ng/mL and 10 ng/mL, but PSA levels vary with age. Age-adjusted normal PSA ranges have been proposed but not standardized or validated.

Screening of men with a life expectancy of fewer than 10 years is unlikely to be useful because most prostate cancer progresses slowly. However, the age range for which screening is most useful is controversial. The ERSPC and Rotterdam trials observed benefits of screening only in men up to about 70 years old.

Interventions

For assessing future prostate cancer risk, numerous studies have demonstrated the association between many genetic and protein biomarker tests and prostate cancer. Commercially available tests for selection of men for initial prostate biopsy include those described in Table 2.

Table 2. Commercially Available Tests to Determine Candidate for Initial Prostate Biopsy

Test	Manufacturer	Description
4Kscore	OPKO lab	Blood test that measures 4 prostate-specific kallikreins, which are combined into an algorithm to produce a risk score estimating the probability of finding high-grade prostate cancer (defined as a Gleason score ≥ 7) if a prostate biopsy were performed.
Prostate Health Index (phi)	Beckman Coulter	Blood immunoassay that combines several components of PSA (total PSA, free PSA, intact PSA, hK2) with an algorithm including patient age, DRE (nodules or no nodules), and a prior negative prostate biopsy.
Mi-Prostate (MiPS)	University of Michigan MLabs	Measures <i>TMPRSS2-ERG</i> gene fusion and calculates a probability score that incorporates serum PSA or the PCPT, and urine <i>TMPRSS2-ERG</i> and <i>PCA3</i> scores
SelectMDx	MDxHealth	Three-gene post-DRE urinary panel for <i>HOXC6</i> and <i>DLX1</i>
ExoDx Prostate IntelliScore (EPI)	Exome Diagnostics	Urine panel for <i>PCA3</i> , <i>ERG</i> , and <i>SPDEF</i> RNA expression in exosomes
Apifyn	Armune BioScience (acquired by Exact Sciences in 2017)	Algorithm with detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2) in serum
PCA3 score (eg Progenesa)	<ul style="list-style-type: none"> Hologic Gen-Probe Many labs offer PCA3 tests (eg, ARUP Laboratories, Mayo Medical Laboratories, LabCorp) 	Measures <i>PCA3</i> mRNA in urine samples after prostate massage. <i>PCA3</i> mRNA may be normalized using PSA level to account for prostate cells.

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DRE: digital rectal exam; hK2: human kallikrein 2 (kallikreins are a subgroup of enzymes that cleave peptide bonds in proteins); PCPT: Prostate Cancer Prevention Trial; PSA: prostate-specific antigen.

Prostate-specific kallikreins (eg, 4Kscore) are a subgroup of enzymes that cleave peptide bonds in proteins. The intact PSA and human kallikrein 2 (hK2) tests are immunoassays that employ distinct mouse monoclonal antibodies. The score combines the measurement of 4 prostate-specific kallikreins (total PSA, free PSA, intact PSA, hK2), with an algorithm including patient age, DRE (nodules or no nodules), and a prior negative prostate biopsy. The 4K algorithm generates a risk score estimating the probability of finding high-grade prostate cancer (defined as a Gleason score ≥ 7) if a prostate biopsy were performed. The intended use of the test is to aid in a decision whether to proceed with a prostate biopsy. The test is not intended for patients with a previous diagnosis of prostate cancer, who have had a DRE in the previous 4 days, who have received 5 α reductase inhibitor therapy in the previous 6 months, or who have undergone treatment for symptomatic benign prostatic hypertrophy in the previous 6 months.

The Prostate Health Index (phi; Beckman Coulter) is an assay that combines results of 3 blood serum immunoassays (total PSA, free PSA, [-2]proPSA [p2PSA]) numerically to produce a "phi score." This score is calculated with the phi algorithm using the following formula: $([-2]proPSA/free\ PSA) \times \sqrt{total\ PSA}$. The phi score is indicated for men 50 years and older with above-normal total PSA readings between 4.0 ng/mL and 10 ng/mL who have had a negative DRE in order to distinguish prostate cancer from benign prostatic conditions.

TMPRSS2 is an androgen-regulated transmembrane serine protease that is preferentially expressed in the normal prostate tissue. In prostate cancer, it may be fused to an E26 transformation-specific (ETS) family transcription factor (*ERG*, *ETV1*, *ETV4*, *ETV5*), which modulates transcription of target genes involved in cell growth, transformation, and apoptosis. The result of gene fusion with an ETS transcription gene (eg, Mi-Prostate) is that the androgen-responsive promoter of *TMPRSS2* upregulates expression of the ETS gene, suggesting a mechanism for neoplastic transformation. Fusion genes may be detected in tissue, serum, or urine.

TMPRSS2-ERG gene rearrangements have been reported in 50% or more of primary prostate cancer samples. Although *ERG* appears to be the most common ETS family transcription factor involved in the development of fusion genes, not all are associated with *TMPRSS2*. About 6% of observed rearrangements are seen with *SLC45A3*, and about 5% appear to involve other types or rearrangement.

SelectMDx for prostate cancer uses a model that combines *HOXC6* and *DLX1* gene expression with traditional risk assessment models. *HOXC6* and *DLX1* mRNA is measured in post-DRE urine against kallikrein-related peptidase 3 as an internal reference.

ExoDx Prostate (IntelliScore), also called EPI, evaluates a urine-based 3-gene exosome expression assay using *PCA3* and *ERG* RNA in urine, normalized to *SPDEF*. Evidence on the association between the *PCA3* gene and prostate cancer aggressiveness is described in the next section on repeat biopsy. Measurement

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in exosomes, which are small double-lipid membrane vesicles that are secreted from cells, is novel. Exosomes encapsulate a portion of the parent cell cytoplasm and contain proteins and mRNA. They are shed into biofluids (eg, blood, urine). This test does not require DRE.

Apifyn uses an algorithm to score the detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2) in serum. The identified biomarkers play a role in processes such as androgen response regulation and cellular structural integrity and are proteins that are thought to play a role in prostate tumorigenesis.

Comparators

Standard clinical examination for determining who requires a biopsy might include DRE, review of the history of PSA levels, along with consideration of risk factors such as age, race, and family history. The ratio of free (or unbound) PSA to total PSA (percent free PSA) is lower in men who have prostate cancer than in those who do not. A percent free PSA cutoff of 25% has been shown to have a sensitivity and specificity of 95% and 20%, respectively, for men with total PSA levels between 4.0 ng/mL and 10.0 ng/mL.

The best way to combine all risk information to determine who should go to biopsy is not standardized. Risk algorithms have been developed that incorporate clinical risk factors into a risk score or probability. Two examples are the Prostate Cancer Prevention Trial (PCPT) predictive model and the Rotterdam Prostate Cancer risk calculator (also known as the ERSPC-Risk Calculator 4 [ERSPC-RC]). The American Urological Association and the Society of Abdominal Radiology (2016) recommended that high-quality prostate magnetic resonance imaging, if available, should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy.

Outcomes

The beneficial outcome of the test is to avoid a negative biopsy for prostate cancer. A harmful outcome is a failure to undergo a biopsy that would be positive for prostate cancer, especially when the disease is advanced or aggressive. Thus the relevant measures of clinical validity are the sensitivity and negative predictive value (NPV). The appropriate reference standard is a biopsy, though prostate biopsy is an imperfect diagnostic tool. Biopsies can miss cancers and repeat biopsies are sometimes needed to confirm the diagnosis. Detection rates vary by biopsy method and patient characteristics.

Timing

The timeframe of interest for calculating performance characteristics is time to biopsy result. Men who forgo biopsy based on test results could miss or delay the diagnosis of cancer. Longer follow-up would be necessary to determine the effects on overall survival.

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Setting

Initial screening using PSA levels and DRE may be performed in the primary care setting with referral to specialists (urologists) for suspicious findings and biopsy. Clinical practice on screening methods and frequency vary widely.

Study Selection Criteria

For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Studies were excluded from the evaluation of the clinical validity of the test because they did not use the marketed version of the test, did not include information needed to calculate performance characteristics, did not use an appropriate reference standard or reference standard was unclear, did not adequately describe the patient characteristics or did not adequately describe patient selection criteria.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Kallikreins Biomarkers and 4Kscore Test

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Russo et al (2017) performed a systematic review of studies that evaluated the diagnostic accuracy of the 4Kscore test in patients undergoing biopsy with a PSA level between 2 ng/mL and 20 ng/mL (see Table 3). Results of the DRE were not described. The NPV to exclude any type of cancer ranged from 28% to 64% (see Table 4). The NPV of the 4Kscore test to exclude high-grade (Gleason score ≥ 7) cancer ranged from 95% to 99%.

Table 3. Characteristics of Systematic Reviews Assessing the Clinical Validity of the 4Kscore for Diagnosing Prostate Cancer

Study	Studies	Dates	Key Inclusion Criteria ^a	Design	Reference Studies Included	Comments
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Russo et al (2017) ²⁷	10	2010-2015	Blood samples were collected before biopsy; indication for biopsy was independent of 4K results	Mostly prospective, observational	Biopsy for prostate cancer detection (overall or high grade with Gleason score ≥ 7)	PSA range, 2-20 ng/mL
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PSA: prostate-specific antigen.

Table 4. Results of Systematic Reviews Assessing the Clinical Validity of 4Kscore for Diagnosing Prostate Cancer

Study	Studies	N (Range)	Outcomes	Sens (95% CI), %	Spec (95% CI), %	PPV Range %	NPV Range %	OR (95% CI)
Russo et al (2017) ²⁷	10	NR	Diagnostic performance for any prostate cancer	74 (73 to 76)	60 (59 to 61)	59-92	28-64	4.6 (3.5 to 6.1)
Russo et al (2017) ²⁷ (subgroup analysis)	10	NR	Diagnostic performance for high-grade prostate cancer	87 (85 to 89)	61 (60 to 62)	8-43	95-99	10.2 (8.1 to 12.8)

CI: confidence interval; NR: not reported; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Prospective Studies

The performance of the 4Kscore test was validated in 1012 patients enrolled in a blinded, prospective study of all patients scheduled for a prostate biopsy at 26 urology centers in the United States (see Tables 5 and 6). As reported by Parekh et al (2015), biopsies were negative in 54% (n=542) of cases, and showed low-grade (all Gleason grade 6) prostatic cancer in 24% (n=239) and high-grade cancer in 23% (n=231) of cases. Statistical analysis of 4Kscore test clinical data had an area under the receiving operating curve of 0.82 for the detection of high-grade prostate cancer; the area under the receiving operating curve for the PCPT risk calculator model was 0.74, but a precision estimate was not given.

Longer term data on the incidence of prostate cancer in men who do not have a biopsy following testing with the marketed version of 4Kscore are not available. However, a case-control study by Stattin et al (2015), which was a nested cohort study of more than 17,000 Swedish men, estimated that, for men ages 60 with PSA levels of 3 or higher and a kallikrein-related peptidase 3 risk score less than 10%, the risk of metastasis at 20 years was 1.95% (95% CI, 0.64% to 4.66%).

Table 5. Characteristics of Clinical Validity Studies Assessing the 4Kscore Test

Study	Study Population	Design ^a	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors	Comment ^b
Parekh et al (2015) ²⁸ (U.S.)	Patients scheduled for a prostate biopsy independent of age, PSA level, DRE, or	Prospective, 26 U.S. centers	Prostate biopsy with ≥ 10 cores	Blood sample taken prior to biopsy	Yes	247 (24%) men had an abnormal DRE, 348 (34%) had PSA level < 4 ng/mL, and

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prior prostate biopsy

104 (10%) had PSA level >10 ng/mL

DRE: digital rectal exam; NR: not reported; PSA: prostate-specific antigen.

Table 6. Clinical Validity Studies Assessing the 4Kscore Test

Study	Initial N	Final N	Performance Characteristics (95% CI)	
			4Kscore	Comparators
Parekh et al (2015) ²⁸ (U.S.)	1012		AUC=0.82 (0.79 to 0.85)	<ul style="list-style-type: none"> Risk model without intact PSA and hK2 AUC=0.75 (0.71 to 0.79)
				<ul style="list-style-type: none"> PCPT modified risk calculator^a AUC=0.74 (NR)

AUC: area under the curve; CI: confidence interval; NR: not reported; PCPT: Prostate Cancer Prevention Trial; PSA: prostate-specific antigen.

^a Excluding the term for family history because it was not known in this cohort.

The purpose of the gaps tables (see Tables 7 and 8) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 7. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Parekh et al (2015) ²⁸ (U.S.)	4. Study population included patients outside of the indeterminate range of PSA				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. PSA: prostate-specific antigen.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 8. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Parekh et al (2015) ²⁸ (U.S.)						1. Study did not provide confidence intervals of validity vs the standard clinical models

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

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^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Subsection Summary: Clinically Valid

There is uncertainty regarding clinical performance characteristics such as sensitivity, specificity, and predictive value due to the following factors: a lack of standardization of cutoffs to recommend biopsy, study populations including men with low (<4 ng/mL) and high (>10 ng/mL) baseline PSA levels, positive DRE results likely outside the intended use population, and lack of comparison with models using information from standard clinical examination. Very few data are available on longer-term clinical outcomes of men who are not biopsied based on 4Kscore results. The evidence needed to conclude the test has clinical validity is insufficient.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No RCTs reporting direct evidence of utility for clinical outcomes were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Various cutoffs for the kallikrein-related peptidase 3 probability score were used in decision-curve analyses to estimate the number of biopsies vs cancers missed. Parekh et al (2015) estimated that 307 biopsies could have been avoided and 24 cancer diagnoses would have been delayed with a 9% 4Kscore cutoff for biopsy, and 591 biopsies would have been avoided with 48 diagnoses delayed with a 15% cutoff.²⁸ However, inferences on clinical utility cannot be made due to deficiencies in estimating the clinical validity that is described in the previous section.

Konety et al (2015) reported on results of a survey of 35 U.S. urologists identified through the 4Kscore database at OPKO Lab as belonging to practices that were large users of the test. All 611 patients of participating urologists to whom men were referred for abnormal PSA level or DRE and had a 4Kscore test

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were included. Urologists, who received the 4Kscore as a continuous risk percentage, were retrospectively asked about their plans for biopsy before and after receiving the test results and whether the 4Kscore test results influenced their decisions. The physicians reported that the 4Kscore results influenced decisions in 89% of men and led to a 64.6% reduction in prostate biopsies. The 4Kscore risk categories (low risk: <7.5%, intermediate risk: 7.5%-19.9%, high risk: ≥20%) correlated highly (p<0.001) with biopsy outcomes in 171 men with biopsy results.

Section Summary: Kallikreins Biomarkers and 4Kscore Test

Absent direct evidence of clinical utility, a chain of evidence might be constructed. The 4Kscore test is associated with a diagnosis of aggressive prostate cancer. The incremental value of the 4Kscore concerning clinical examination and risk calculators in the intended use population is unknown due to deficiencies in estimating clinical validity. There is no prospective evidence that use of 4Kscore changes management decisions. Given that the test manufacturer’s website states the test is for men with inconclusive results, the inclusion of men with PSA levels greater than 10 ng/mL and positive DRE in the validation studies are likely not reflective of the intended use population. The chain of evidence is incomplete.

proPSA and Prostate Health Index

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Several systematic reviews and meta-analyses have evaluated the clinical validity of p2PSA (proPSA) and phi tests. The characteristics of the most comprehensive reviews from 2016 and 2017 are shown in Table 9. All primary studies were observational and most were retrospective. Reviews included studies of men with a positive, negative, or inconclusive DRE; Pecoraro et al (2016) restricted eligibility to studies including PSA levels between 2 ng/mL and 10 ng/mL, while Russo et al (2017) restricted eligibility to studies including PSA levels between 2 ng/mL and 20 ng/mL.

Pecoraro et al (2016) rated most of the 17 primary studies as low quality due to the design (most were retrospective), lack of blinding of outcome assessors to reference standard results, lack of clear cutoffs for diagnosis, and lack of explicit diagnostic question. Russo et al (2017) included 23 studies that were mostly prospective and rated as moderate quality. There was high heterogeneity across studies but pooled estimates showed generally low NPV (5% to 63%) and low specificity (25% to 35%) when sensitivity was 90% to 93% (see Table 10).

Table 9. Characteristics of Systematic Reviews Assessing the Clinical Validity of the phi Test for Diagnosing Prostate Cancer

Study	Studies	Dates	Key Inclusion Criteria ^a	Design	Reference Studies
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Included				Included	
Pecoraro et al (2016) ³¹	17	2003-2014	PSA level 2-10 ng/mL	Prospective, retrospective, and mixed prospective/retrospective, observational	
Russo et al (2017) ²⁷	23	2010-2015	Blood samples were collected before biopsy; PSA level 2-20 ng/mL; indication for biopsy was independent of phi results	Mostly prospective, observational	Biopsy for prostate cancer detection (overall or high grade with Gleason score ≥ 7)

PSA: prostate-specific antigen.

^a Results from all studies were with or without digital rectal exam.

Table 10. Results of Systematic Reviews on the Clinical Validity of the phi Test for Diagnosing Prostate Cancer

Study	Studies/N (Range)	Outcomes	Sens (95% CI), %	Spec (95% CI), %	PPV Range, %	NPV Range, %	OR (95% CI), %
Pecoraro et al (2016) ³¹	17/6912 (63-1091)	Diagnostic performance for any prostate cancer	Set at 90	Phi: 31 (29 to 33) Total PSA: 25 (23 to 27)			
Russo et al (2017) ²⁷	23	Diagnostic performance for any prostate cancer	89 (88 to 90)	34 (32 to 35)	76-98	15-63	4.4 (3.3 to 5.8)
Russo et al (2017) ²⁷ (subset)	7	Diagnostic performance for high grade prostate cancer	93 (90 to 95)	26 (25 to 28)	88-99	5-31	3.5 (2.5 to 5.0)
Summary			88 to 95	25 to 35	76-99	5-63	

AUC: area under the curve; CI: confidence interval; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; PSA: prostate-specific antigen; Sens: sensitivity; Spec: specificity.

Subsection Summary: Clinically Valid

Many studies and systematic reviews of these studies have reported on the clinical validity of phi. Primary studies included men with positive, negative, and inconclusive DRE and men with PSA levels outside of the 4- to 10-ng/mL range. There is no standardization of cutoffs used in a clinical setting for diagnosis. With sensitivity around 90% for the detection of any prostate cancer, specificity ranged from 25% to 35% and NPV, which would indicate an absence of disease and allow patients to forgo biopsy, ranged from 5% to 63%. For high-grade disease, the sensitivity of the phi test was 93%, with an NPV ranging from 5% to 31%.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs directly measuring the effect of the phi test on clinical outcomes were found.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence might be used to demonstrate clinical utility if each link in the chain is intact. Two observational studies have shown a reduction or delay in biopsy procedures for men with PSA levels in the 4 to 10 ng/mL range, nonsuspicious DRE findings, and a low phi score. Tosoian et al (2017) found a 9% reduction in the rate of biopsy of 345 men who underwent phi testing compared with 1318 men who did not. There was an associated 8% reduction in the incidence of negative biopsies in men who had phi testing, but interpretation of results is limited because the use of the phi test was based solely on provider discretion. A prospective multicenter study by White et al (2018) evaluated physician recommendations for biopsy before and after receiving the phi test result. The phi score affected the physician's management plan in 73% of cases, with biopsy deferrals when the phi score was low and the decision to perform biopsies when the phi score was 36 or more. A chain of evidence requires evidence that the test could be used to affect health outcomes, and that the test is clinically valid. Due to questions about the clinical validity of the test, a chain of evidence cannot be constructed.

Section Summary: proPSA and Prostate Health Index

The phi test is associated with a diagnosis of prostate cancer. Although observational studies have shown a reduction or delay in a biopsy with phi testing, a chain of evidence cannot be constructed about an improvement in health outcomes due to limitations in clinical validity. The chain of evidence is incomplete.

TMPRSS Fusion Genes and Mi-Prostate Score

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Validation studies on the combined 2-gene test (*TMPRSS2-ERG* and *PCA3*) are shown in Table 11. Sanda et al (2017), from the National Cancer Institute Early Detection Research Network, reported separate developmental and validation cohorts for high-grade prostate cancer in men undergoing initial prostate biopsy. For the validation cohort, any of the following was considered a positive result: PSA level greater than 10 ng/mL, urine *TMPRSS2-ERG* score greater than 8, or urine *PCA3* score greater than 20. Performance characteristics of this algorithm, compared with the individual markers, are shown in Table 12.

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Analysis showed that specificity could be increased from 17% to 33% compared with PSA alone, without loss of sensitivity. The difference in specificity was statistically significant, with a prespecified 1-sided p value of 0.04 (lower bound of 1-sided 95% CI, 0.73%).

In the study by Tomlins et al (2016), 80% of the 1244 patients were undergoing initial biopsy due to elevated PSA levels (see Table 11). Thresholds were not defined and the AUCs for predicting any cancer using PSA alone, PCPT risk calculator alone, or the Mi-Prostate Score (MiPS) alone are shown in Table 12. The AUC for MiPS was significantly improved compared with the PCPT risk calculator (p<0.001).

Table 11. Characteristics of Studies Assessing the Clinical Validity of the Combined *TMPRSS2-ERG* and *PCA3* Score

Study; Trial	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Sanda et al (2017) ³⁴ ; (NCI-EDRN)	561 men who had initial prostate biopsy	4-center PProBE criteria	HG (Gleason score ≥7) prostate cancer on biopsy	Algorithm with PSA level >10 ng/mL; <i>T2:ERG</i> score >8; or <i>PCA3</i> score >20	Samples collected after DRE and prior to biopsy	Yes	A separate developmental cohort of 516 men is reported
Tomlins et al (2016) ³⁵	1244 men who had initial (80%) or repeat biopsy due to elevated PSA	7-center prospective	Any cancer or HG cancer (Gleason score ≥7)		Samples collected after DRE and prior to biopsy	Yes	A MiPS score threshold was not provided, so sensitivity and NPV were not calculated

DRE: digital rectal exam; HG; high-grade; NPV: negative predictive value; PSA: prostate-specific antigen; *T2:ERG*: *TMPRSS2-ERG*.

Table 12. Results of Studies Assessing the Clinical Validity of the Combined *TMPRSS2-ERG* and *PCA3* Score

Study	Initial N	Final N	Threshold	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	p ^a
Sanda et al (2017) ³⁴	561	561						
PSA level, ng/mL			3	91.2 (86.6 to 95.8)	16.7 (13.1 to 20.3)	28.2 (28.9 to 29.5)	84.1 (75.1 to 90.3)	
<i>PCA3</i>			7	96.6 (93.7 to 99.5)	18.4 (14.7 to 22.1)	29.8 (28.6 to 30.9)	93.8 (86.2 to 97.3)	
<i>PCA3</i> , <i>T2:ERG</i>			20, 8	90.5 (85.8 to 95.2)	35.4 (30.8 to 40.0)	33.4 (31.5 to 35.4)	91.2 (86.1 to 94.6)	
PSA level >10 ng/mL; <i>T2:ERG</i> score >8; or <i>PCA3</i> score >20				92.6 (88.4 to 96.8)	33.4 (28.8 to 37.9)	33.2 (31.4 to 35.1)	92.6 (87.5 to 95.8)	
AUC (95% CI not reported)								
			Excluded Samples	PSA Alone	PCPT Risk Calculator	PSA Plus <i>PCA3</i>	MiPS	
Tomlins et al (2016) ³⁵	1244	1225	19 with insufficient samples for					

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analysis					
Any cancer	0.59	0.64	0.73	0.75	<0.001
High-grade cancer	0.65	0.71	0.75	0.77	<0.001

AUC: area under the curve; CI: confidence interval; MiPS: Mi-Prostate Score; NPV: negative predictive value; PCPT: Prostate Cancer Prevention Trial; PPV: NPV: positive predictive value; PSA: prostate-specific antigen; Sens: sensitivity; Spec: specificity; T2:ERG: T2:ERG:TMPRSS2-ERG.

^a P value for MiPS vs PCPT risk calculator.

Tables 13 and 14 summarize relevance and design and conduct gaps for each study.

Table 13. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Sanda et al (2017) ³⁴	4. Some patients were 70 y, 16% had an abnormal DRE; median PSA level was 4.8 ng/mL				
Tomlins et al (2016) ³⁵	4. 25% were >70 y, 23% had an abnormal DRE; median PSA level was 4.7 ng/mL		3. Not compared with most current (v2) PCPT risk calculator		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. DRE: digital rectal exam; PCPT: Prostate Cancer Prevention Trial; PSA: prostate-specific antigen.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 14. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Sanda et al (2017) ³⁴ Tomlins et al (2016) ³⁵						1. Confidence intervals not reported

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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Subsection Summary: Clinically Valid

Concomitant detection of *TMPRSS2-ERG* and *PCA3* in addition to the multivariate PCPT risk calculator may more accurately identify men with prostate cancer than with PSA level alone or the PCPT risk calculator alone. However, adding *TMPRSS2-ERG* score to PSA level plus *PCA3* score only resulted in a 0.02 difference in the AUC compared with the combination of PSA plus *PCA3*, with a maximum AUC of 0.77 for the detection of high-grade cancer. In a study from the National Cancer Institute Early Detection Research Network, using either/or thresholds of *TMPRSS2-ERG* plus *PCA3* score or PSA level improved specificity compared with PSA alone, without a loss in sensitivity. It does not appear from this study that an algorithm that combines *TMPRSS2-ERG*, *PCA3*, or PSA level has any incremental improvement in NPV of 92.6% (95% CI, 87.5% to 95.8%) over *PCA3* score alone 93.8% (95% CI, 86.2% to 97.3%).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Sanda et al (2017) calculated that by restricting biopsy to participants with positive findings on *TMPRSS2-ERG* score, *PCA3* score, or PSA level at thresholds of 8, 20, and 10, respectively, would have avoided 42% of unnecessary biopsies (true negative) and 12% of low-grade cancers. It was estimated that 7% of cancers would be missed using the combined threshold, compared with 21% using a *PCA3* threshold of 7.

Tomlins et al (2016) also used decision-curve analysis to estimate the number of biopsies that would have been performed and cancers that would have been missed using a MiPS risk cutoff for biopsy in their cohort. Compared with a biopsy-all strategy, using a MiPS cutoff for aggressive cancer of 15% would have avoided 36% of biopsies while missing 7.0% of any prostate cancer and 1.6% of high-grade prostate cancer diagnoses. Using the PCPT risk calculator cutoff of 15% for aggressive cancer would have avoided 68% of biopsies while missing 25% of any cancer and 8% of high-grade cancer.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

No studies were found that directly show the effects of using MiPS results on clinical outcomes. Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. The

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MiPS test is associated with a diagnosis of prostate cancer and aggressive prostate cancer. The clinical validity study of the MiPS test included men with relevant PSA levels but also included men with positive DRE who would not likely forgo biopsy.

Section Summary: *TMPRSS Fusion Genes and Mi-Prostate Score*

Current evidence on the *TMPRSS2-ERG* and *PCA3* scores is insufficient to support its use. The MiPS test has data suggesting an improved AUC compared with the PCPT risk calculator in a validation study, and improved specificity compared with PSA level in another study, but improvement in diagnostic accuracy compared to individual components of the algorithm at similar thresholds has not been reported. Data on clinical utility are lacking. No prospective data are available on using the MiPS score for decision making. The chain of evidence is incomplete.

SelectMDx for Prostate Cancer

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Van Neste et al (2016) evaluated a risk calculator that added *HOXC6* and *DLX1* expression to a clinical risk model (see Table 15). A training set in 519 men and an independent validation set in 386 men were assessed. When evaluating the risk model in men who were in the “gray zone” of PSA level between 3 ng/mL and 10 ng/mL, the AUC was significantly higher than a clinical risk model alone, Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) for detection of any cancer or for detection of high-grade cancer (see Table 16). A limitation of this study is the inclusion of men with an abnormal DRE (see Tables 17 and 18), which was the strongest predictor of prostate cancer in the training set (OR=5.53; 95% CI, 2.89 to 10.56). The OR for *HOXC6* and *DLX1* expression in this model was 1.68 (95% CI, 1.38 to 2.05; p<0.003).

Table 15. Characteristics of Clinical Validity Studies Assessing SelectMDx for Prostate Cancer

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Van Neste et al (2016) ³⁶	386 men with PSA level >3 ng/mL scheduled for initial (89%) or repeat biopsy	Prospective	Prostate cancer on biopsy	NR	Urine sample taken after DRE and prior to biopsy	NR	

DRE: digital rectal exam; NR: not reported; PSA: prostate-specific antigen.

Table 16. Results of Clinical Validity Studies Assessing SelectMDx for Prostate Cancer

Study	Total N	N With PSA Level <10 ng/mL	N with No or Low-Grade Cancer	AUC for the Risk Score in Patients With PSA Level <10 ng/mL (95% CI)			p
				Any Cancer	HG Cancer	PCPTRC	
Van Neste et	386	264	226/264	0.90	0.78	0.66	0.001

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al (2016) (0.85 to 0.96) (0.68 to 0.88) (0.57 to 0.75)

AUC: area under the curve; CI: confidence interval; HG; high-grade; PCPTRC: Prostate Cancer Prevention Trial Risk Calculator; PSA: prostate-specific antigen.

Table 17. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Van Neste et al (2016)	4. 31% of men had abnormal DRE				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. DRE: digital rectal exam.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 18. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Van Neste et al (2016)		1. Blinding not reported			1. Inadequate description of indeterminate samples	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Subsection Summary: Clinically Valid

One validation study evaluating the SelectMDx for Prostate Cancer was identified. This study reported that a risk model that added expression of *HOX6* and *DLX1* to a clinical risk model increased the AUC for the detection of high-grade cancer for men who were in the “gray zone,” with a PSA level between 3 ng/mL and 10 ng/mL. A limitation of this study is its inclusion of men with an abnormal DRE, which was the strongest predictor of prostate cancer.

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Louisiana

Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Policy # 00272

Original Effective Date: 10/20/2010

Current Effective Date: 04/01/2019

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No trials were identified that compared health outcomes for patients managed with and without the test.

Van Neste et al (2016) estimated that when using a cutoff of 98% NPV for high-grade (Gleason ≥ 7) prostate cancer, there would be a total reduction in biopsies by 42% and a decrease in unnecessary biopsies by 53%.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Current evidence on clinical validity is insufficient.

Because the clinical validity of SelectMDx for Prostate Cancer has not been established, a chain of evidence supporting the clinical utility of this test cannot be constructed.

Section Summary: SelectMDx for Prostate Cancer

No trials identified have compared health outcomes for patients managed with and without the SelectMDx for Prostate Cancer. A chain of evidence depends on clinical validity. Current evidence on adding *HOXC6* and *DLX1* expression to a clinical risk model is insufficient to support its use. Data on SelectMDx have suggested an improved AUC (0.78) compared with the PCPTRC (0.66) in 1 validation study that included men with PSA levels in the indeterminate range. Sensitivity and specificity rates have not been reported. No prospective data are available on using SelectMDx for decision making. Present studies on clinical validity are insufficient to establish a chain of evidence. The chain of evidence is incomplete.

ExoDx Prostate (IntelliScore)

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

McKiernan et al (2016) conducted a multicenter validation study of urine exosome *PCA3*, *ERG*, and *SPDEF* RNA expression to predict high-grade (Gleason score ≥ 7) prostate cancer (see Table 19). The threshold for

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a positive test was derived from a training set separate from the validation set. The assay improved on the standard of care alone, with an AUC of 0.73 compared with 0.63 for standard of care (p<0.001) and 0.62 for the PCPTRC (see Table 20). Diagnostic performance is shown in Table 20, with sensitivity of 97% and NPV of 96%.

Table 19. Characteristics of Clinical Validity Studies Assessing ExoDx Prostate (IntelliScore)

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
McKiernan et al (2016)	1064 men ≥50 y with PSA level 2-10 ng/mL and scheduled for initial	Multicenter prospective	Gleason score ≥7 prostate cancer on biopsy	15.6 derived from a separate training set	Urine collection prior to biopsy	Yes	

PSA: prostate-specific antigen.

Table 20. Results of Clinical Validity Studies Assessing ExoDx Prostate (IntelliScore)

Study	Initial N	Final N	Excluded Samples	Area Under the Curve (95% CI)			p
				ExoDx + SOC	SOC Alone	PCPTRC	
McKiernan et al (2016)	1064	519 in intended use population	Technical reasons or failure to meet study criteria	0.73 (0.68 to 0.77)	0.63 (0.58 to 0.68)	0.62 (0.57 to 0.67)	<0.001
Diagnostic Performance (95% CI), %							
				Sensitivity	Specificity	PPV	NPV
				97.44 (93.93 to 100)	27.68 (21.09 to 34.28)	37.25 (30.62 to 43.89)	96.08 (90.75 to 100)

CI: confidence interval; NPV: negative predictive value; PSA: prostate-specific antigen; PCPTRC: Prostate Cancer Prevention Trial Risk Calculator; PPV: positive predictive value; SOC: standard of care.

Tables 21 and 22 summarize relevance and design and conduct gaps in each study.

Table 21. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
McKiernan et al (2016)	4. Study population included patients with suspicious DRE		3. Standard of care did not include DRE or free PSA results		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. DRE: digital rectal exam; PSA: prostate-specific antigen.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

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^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 22. Study Design and Conduct Gaps

Study	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
McKiernan et al (2016)			1. The timing of urine sampling was not described			

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Subsection Summary: Clinically Valid

The ExoDx Prostate (IntelliScore) assay showed a sensitivity of 97% and NPV of 96% for high-grade prostate cancer in men over 50 who had PSA levels between 2 ng/mL and 10 ng/mL. The primary limitation of the study was that patients with a suspicious DRE were enrolled in the study, but DRE or free PSA were not included in the comparison prediction.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were identified that compared health outcomes for patients managed with and without the test.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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McKeirnan et al (2016) calculated that using a predefined cut point, 138 (27%) of 519 biopsies would have been avoided, missing 8% of patients with high-risk disease. Present studies on clinical validity are insufficient to establish a chain of evidence.

Section Summary: ExoDx Prostate (IntelliScore)

No trials were identified that compared health outcomes for patients managed with and without the ExoDx Prostate. A chain of evidence depends on clinical validity. Current evidence on adding exosome *PCA3* and *ERG* to a clinical risk model is insufficient to support its use. ExoDx Prostate has data suggesting an improved AUC (0.73) compared with the standard of care (0.63) in 1 validation study. That study included men with PSA levels in the indeterminate range. However, the study also included men with suspicious DRE and the comparator did not include DRE in its score. The sensitivity and NPV at the defined threshold were 97% and 96%, respectively. No prospective data are available on using ExoDx Prostate for decision making. Present studies on clinical validity are insufficient to establish a chain of evidence.

Apifiny

Schipper et al (2015) identified 8 autoantibodies associated with prostate cancer in a case-control study of men 40 to 70 years old with prostate cancer and PSA levels between 2.5 ng/mL and 20 ng/mL, compared to healthy men 25 to 40 years of age with PSA levels less than 1.0 ng/mL. When the algorithm was applied to an independent validation set, the AUC was 0.69 (95% CI, 0.62 to 0.75).

Section Summary: Apifiny

Evidence on Apifiny is preliminary. In a validation set, the AUC was 0.69. The threshold for a positive test has not been determined and the sensitivity, specificity, PPV, and NPV rates compared with established tests have not been reported. Studies validating the diagnostic performance of Apifiny are needed.

PCA3 Score (eg, ProgenSA PCA3 Assay)

Some studies have assessed men who are scheduled for an initial biopsy, although the Food and Drug Administration–approved indication for the ProgenSA PCA3 Assay is to aid in the decision for repeat biopsy in men 50 years or older who have had one or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on current standard of care. Evaluation of the PCA3 score is relevant to both initial and repeat prostate biopsy.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Several systematic reviews and meta-analyses have described the clinical validity of the ProgenSA PCA3 Assay. The characteristics of the reviews are described in Table 23. All primary studies were observational, with 1 study using the placebo arm from an RCT. Reviewers selected studies of men with positive,

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negative, or inconclusive DRE without restrictions on PSA levels. Cui et al (2016) reported on results of a systematic review of case-control or cohort studies. The studies assessed both initial and repeat biopsy and had a quality rating of moderate to high. The assessment by Nicholson et al (2015) for the National Institute for Health and Care Excellence included 11 cohorts of men for whom initial prostate biopsy results were negative or equivocal.

Results from the systematic reviews are shown in Table 24. In the meta-analysis by Cui et al (2016), the most common PCA3 assay cutoff for categorizing low and high risk was 35 (25 of 46 studies). The estimates of AUC were lower for studies that included men having repeated (0.68) vs initial (0.80) biopsies. Nicholson et al (2015) included 13 reports describing 11 cohorts, including one from the placebo arm of an RCT. Referral criteria for repeat biopsy were varied, often unclear, and differed based on whether normal or abnormal DREs were included. The mean or median PSA, when reported, ranged from 4.9 to 11.0 ng/mL and the prevalence of cancer on repeat biopsy varied from 11.4% to 68.3%. Meta-analyses were not performed due to heterogeneity. The addition of PCA3 to clinical assessment, as a continuous or categorical variable, generally led to improvement in AUC, but studies that fixed sensitivity and derived specificity and those that reported decision-curve analysis had mixed results.

Table 23. Characteristics of Systematic Reviews Assessing the Clinical Validity of ProgenSA PCA3 Assay for Diagnosing Prostate Cancer

Study	Studies	Dates	Key Inclusion Criteria	Design	Reference Studies Included
Cui et al (2016)	46	Up to 2014		Prospective, retrospective (case-control or cohort) OBS	Biopsy as reference standard
Nicholson et al (2015)	11	2000-2014	Initial prostate biopsy negative or equivocal, 6+ cores in initial biopsy, with or without DRE	Prospective and mixed (prospective/retrospective) OBS (1 included a cohort from an RCT)	Biopsy as reference standard

DRE: digital rectal exam; OBS: observational; RCT: randomized controlled trial.

Table 24. Results of Systematic Reviews Assessing the Clinical Validity of ProgenSA PCA3 Assay for Diagnosing Prostate Cancer

Study	Studies	N (Range)	Outcomes	Sens (95% CI), %	Spec (95% CI), %	AUC (95% CI) or Range
Cui et al (2016)	46	12,295 (NR)	Any prostate cancer on initial or repeat biopsy	Pooled: 65% (63% to 66%) Range: 47%-95%	<ul style="list-style-type: none"> • Pooled: 73% (72% to 74%) • Range: 22%-100% 	0.75 (0.74 to 0.77)
Nicholson et al (2015)	11	3336 (41-1072)	Any prostate cancer on repeat biopsy	CA alone range, 44%-48% CA plus PCA3 range, 39%-46%	Fixed at 80%	<ul style="list-style-type: none"> • CA alone: 0.55-0.75 • CA plus PCA3: 0.61-0.76

AUC: area under the curve; CA: clinical assessment; CI: confidence interval; NR: not reported; Sens: sensitivity; Spec: specificity.

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Prospective Studies

Not included in the systematic reviews was a prospective trial from the National Cancer Institute on the clinical validity of the PCA3 assay to complement PSA-based detection of prostate cancer (see Table 25).

The trial was designed to evaluate whether PCA3 greater than 60 could improve the PPV of an initial biopsy and whether PCA3 less than 20 could improve the NPV of a repeat biopsy. Of the 859 men in the study, 562 were presenting for their initial prostate biopsy and 297 were presenting for repeat biopsy. For the detection of high-grade cancer, the performance of PCPT risk calculator was modestly improved by adding PCA3 assay results to the risk calculator factors, with an AUC improvement from 0.74 to 0.78 for initial biopsy and 0.74 to 0.79 on repeat biopsy ($p \leq 0.003$). The PPV of the PCA3 assay at a threshold of 60 ng/mL to detect prostate cancer in an initial biopsy was 80% (95% CI, 72% to 86%), while the NPV of the PCA3 assay at a threshold of 20 ng/mL for prostate cancer in men undergoing repeat biopsy was 88% (95% CI, 81% to 93%; see Table 26). Estimates of biopsies avoided and cancer missed at this threshold is described in the section on clinical utility.

Table 25. Characteristics of Clinical Validity Studies Assessing the ProgenSA PCA3 Assay

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Wei et al (2014)	910 men scheduled for a diagnostic prostate biopsy (initial or repeat)	Prospective	Any prostate cancer on biopsy or HG prostate cancer (Gleason score >6)	Determined a priori at thresholds of <20 and >60	Urine samples collected following DRE and prior to biopsy	Yes	

DRE: digital rectal exam; HG: high-grade.

Table 26. Results of Clinical Validity Studies Assessing the ProgenSA PCA3 Assay

Study	Initial N	Final N	Excluded Samples	Clinical Validity (95% Confidence Interval), %			
				Sensitivity	Specificity	PPV	NPV
Wei et al (2014) ⁴¹							
Initial biopsy PCA3 >60	910	859	27	42 (36 to 48)	91 (87 to 94)	80 (72 to 86)	
Repeat biopsy PCA3 <20		297		76 (64 to 86)	52 (45 to 58)		88 (81 to 93)

NPV: negative predictive value; PPV: positive predictive value.

No notable gaps were identified for relevance or design and conduct.

Subsection Summary: Clinically Valid

At least 47 studies have evaluated the clinical validity of PCA3 mRNA to facilitate decision making for initial or repeat prostate biopsy, and there are systematic reviews of those studies. Studies of the PCA3 score as

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a diagnostic test for prostate cancer have reported sensitivities and specificities in the moderate range (eg, 76% sensitivity, 52% specificity). One systematic review that focused on studies of repeat biopsy found mixed results regarding whether the PCA3 assay could improve diagnostic accuracy over clinical assessment alone. Another systematic review found an AUC of 0.68 for the PCA3 assay in men having repeat biopsies.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Clinical utility studies using assay results for decision making for initial biopsy, repeat biopsy, or treatment have not been reported, nor have studies of the effects of using assay results on clinical outcomes.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Several studies using decision analysis to estimate the cost-benefit tradeoff between reduction in unnecessary biopsies and missed prostate cancers have been published. One group reported potential reductions in unnecessary biopsies of 48% to 52%, with attendant increases in missed prostate cancers of 6% to 15% using either a PCA3-based nomogram or PCA3 level corrected for prostate volume (PCA3 density). Merdan et al (2015) used decision analysis to simulate long-term outcomes associated with use of the PCA3 score to trigger repeat biopsy compared with the PCPT risk calculator in men with at least 1 previous negative biopsy and elevated PSA levels. They estimated that incorporating the PCA3 score of 25 (biopsy threshold) into the decision to recommend repeat biopsy could avoid 55.4% of repeat biopsies, with a 0.93% reduction in the 10-year survival rate. Wei et al (2014) calculated that for men with a PCA3 score less than 20 and PSA less than 4 ng/mL, 8% of men would have avoided a repeat biopsy with 9% of low-grade cancers missed and no high-grade cancers missed. If only PCA3 scores less than 20 were taken into account, 46% of men would have avoided rebiopsy but 12% would have undiagnosed cancer and 3% would have undiagnosed high-grade cancer. For patients undergoing an initial biopsy, 13% of aggressive cancers would have been underdiagnosed.

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Section Summary: PCA3 Score (eg, Progenesa PCA3 Assay)

Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. Studies of the PCA3 score as a diagnostic test for prostate cancer have reported sensitivities and specificities in the moderate range. Consideration of rebiopsy based only on PCA3 scores was estimated to miss 3% of aggressive cancers. One estimate suggested that adding a PCA3 score to PSA level would reduce rebiopsy rates by 8%, while another analysis suggested that over half of rebiopsies could be avoided by adding the PCA3 score to the PCPT risk calculator. No prospective studies were found describing differences in management based on PCA3 risk assessment. The clinical utility of the PCA3 test is uncertain because it is not clear whether its use can change management in ways that improve patient outcomes. The chain of evidence is incomplete.

BIOMARKER TESTING FOR SELECTION OF MEN FOR REPEAT PROSTATE BIOPSY

Clinical Context and Test Purpose

The purpose of genetic and protein biomarker testing for prostate cancer is to inform the selection of men who should undergo repeat biopsy. The conventional decision-making tools for identifying men for prostate biopsy include DRE, serum PSA, and patient risk factors such as age, race, and family history of prostate cancer are described in the previous section on selecting men for initial prostate biopsy.

Given the risk, discomfort, burden of biopsy, and the low diagnostic yield, there is a need for noninvasive tests that distinguish potentially aggressive tumors that should be referred for rebiopsy from clinically insignificant localized tumors or other prostatic conditions that do not need rebiopsy, with the goal of avoiding low-yield biopsy.

The question addressed in this evidence review is: Does the use of testing for genetic protein biomarkers improve the net health outcome in men being considered for a repeat prostate biopsy?

The following PICOTS were used to select literature that provides evidence relevant to this review.

Patients

The relevant population is men for whom a rebiopsy is being considered because the results of an initial prostate biopsy were negative or equivocal and other clinical symptoms remain suspicious.

Interventions

For assessing future prostate cancer risk, numerous studies have demonstrated the association between many genetic and protein biomarker tests and prostate cancer. Commercially available tests for selection of men for repeat prostate biopsy include those described in Table 27.

Table 27. Commercially Available Tests to Determine Candidates for Repeat Prostate Biopsy

Test	Manufacturer	Description
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Test	Manufacturer	Description
PCA3 Score (eg, ProgenSA PCA3 Assay)	<ul style="list-style-type: none"> Hologic Gen-Probe Many labs offer PCA3 tests (eg, ARUP Laboratories, Mayo Medical Laboratories, LabCorp) 	Measures PCA3 mRNA in urine samples after prostate massage. PCA3 mRNA may be normalized using PSA to account for prostate cells.
ConfirmMDx	MDxHealth	Measures methylation of the genes <i>GSTP1</i> , <i>APC</i> , and <i>RASSF1</i> in tissue sample
Prostate Core Mitomics Test (PCMT)	Mitomics (formerly Genesis Genomics)	Measures deletions in mitochondrial DNA by polymerase chain reaction in tissue sample
Gene panel testing	Many labs offer SNV testing, such as Life Technologies, LabCorp (23andme), and ARUP Laboratories (deCODE)	Panel tests for prostate cancer risk are offered as laboratory-developed tests

PCA3: prostate cancer antigen 3; PSA: prostate-specific antigen; SNV: single nucleotide variant.

Prostate cancer antigen 3 (PCA3) is a noncoding long chain RNA that is highly overexpressed in prostate cancer compared with noncancerous prostate tissue and is detectable in urine. The ProgenSA PCA3 Assay is approved by the Food and Drug Administration to facilitate decision making among men with prior negative prostate biopsies.

Epigenetic changes—chromatin protein modifications that do not involve changes to the underlying DNA sequence but can change gene expression—have been identified in specific genes. An extensive literature has reported significant associations between epigenetic DNA modifications and prostate cancer. ConfirmMDx (MDxHealth) is a commercially available test for gene methylation intended to distinguish true-from false-negative prostate biopsies to avoid the need for repeat biopsy.

The Prostate Core Mitomics Test (PCMT; Mitomics; formerly Genesis Genomics) is a proprietary test intended to determine whether a patient has prostate cancer, despite a negative prostate biopsy, by assessing a 3.4-kilobases deletion in mitochondrial DNA by polymerase chain reaction to detect “tumor field effect.” The test is performed on the initial negative prostate biopsy tissue and is being evaluated in men who have had an initial negative biopsy. A negative PCMT result is intended to confirm the result of the negative biopsy so that the patient can avoid a second biopsy, while a positive PCMT is intended to indicate that the patient is at high risk of undiagnosed prostate cancer.

SNVs occur when a single nucleotide is replaced with another, and they are the most common type of genetic variation in humans. They occur normally throughout the genome and can act as biologic markers for disease association. Genome-wide association studies have identified correlations between prostate cancer risk and specific SNVs. However, it is widely accepted that, individually, SNV-associated disease risk is low and of no value in screening for disease, although multiple SNVs in combination may account for a higher proportion of prostate cancer. Investigators have begun to explore the use of algorithms incorporating information from multiple SNVs to increase the clinical value of testing.

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Comparators

Standard clinical examination for determining who requires a biopsy might include DRE, review of the history of PSA values, along with consideration of risk factors such as age, race, and family history. The ratio of free (unbound) PSA to total PSA is lower in men who have prostate cancer than in those who do not. A percent free PSA cutoff of 25% has been shown to have a sensitivity and specificity of 95% and 20%, respectively, for men with total PSA levels between 4.0 ng/mL and 10.0 ng/mL.

The best way to combine all of the risk information to determine who should go to biopsy is not standardized. Risk algorithms have been developed that incorporate clinical risk factors into a risk score or probability. Two examples are the PCPT predictive model and the ERSPC-RC. The American Urological Association and the Society of Abdominal Radiology recently recommended that high-quality prostate magnetic resonance imaging, if available, should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is under evaluation for a possible repeat biopsy.

Outcomes

The beneficial outcome of the test is to avoid a negative biopsy for prostate cancer. A harmful outcome is failure to undergo a biopsy that would be positive for prostate cancer, especially when the disease is advanced or aggressive. Thus, the relevant measures of clinical validity are the sensitivity and NPV. The appropriate reference standard is a biopsy, though prostate biopsy is an imperfect diagnostic tool. Biopsies can miss cancers and repeat biopsies are sometimes needed to confirm the diagnosis. Detection rates vary by biopsy method and patient characteristics, with published estimates between 10% and 28% for a second biopsy and 5% and 10% for a third biopsy.

Timing

The timeframe of interest for calculating performance characteristics is time to biopsy result. Men who forgo biopsy based on test results could miss or delay the diagnosis of cancer. Longer follow-up would be necessary to determine the effects on overall survival.

Setting

Screening using PSA levels and DRE may be performed in the primary care setting with referral to specialists (urologists) for suspicious findings and biopsy. Clinical practice on screening methods and frequency vary widely.

Study Selection Criteria

For the evaluation of clinical validity, studies that met the eligibility criteria outlined for the initial biopsy indication were considered.

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Gene Hypermethylation and ConfirmMDx

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Three blinded multicenter validation studies of the ConfirmMDx test have been performed, one of which was conducted in African American men (see Table 28). For the cases that had a positive second biopsy after an initial negative biopsy, sensitivity ranged from 62% to 74%, with an NPV for a negative second biopsy ranging from 79% to 90% (see Table 29). Multivariate analysis of potential predictors of cancer on repeat biopsy, corrected for age, PSA, DRE, first biopsy histopathology characteristics, showed that the ConfirmMDx test was the most significant independent predictor of patient outcome in both DOCUMENT (OR=2.69; 95% CI, 1.60 to 4.51) and MATLOC (OR=3.17; 95% CI, 1.81 to 5.53) studies.

Van Neste et al (2016) and Partin et al (2016) reported on results of combined data from the DOCUMENT and MATLOC studies for patients with high-grade (Gleason score, ≥ 7) prostate cancer. DNA methylation was the most significant and important predictor of high-grade cancer, with an NPV of 96% (precision not reported) and an OR of 9.80 (95% CI, 2.12 to 45.23).

Table 28. Characteristics of Clinical Validity Studies Assessing ConfirmMDx

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors	Comment
Waterhouse et al (2018)	Archived, cancer-negative prostate biopsy core tissue samples from 211 African American men from 7 U.S. urology centers	Retrospective, ConfirmMDx performed on first biopsy	Repeat biopsy	NR	<30 mo	Yes	55% of men had a normal DRE; median PSA level was 6.2 ng/mL
Partin et al (2014) DOCUMENT	Archived, cancer-negative prostate biopsy core tissue samples from 350 men from 5 U.S. urology centers	Retrospective, case-control with assay performed on archived samples	Repeat biopsy	NR	<24 mo	Yes	60% of men had a normal DRE; median PSA level was 5.3 ng/mL
Stewart et al (2013) MATLOC	Archived cancer-negative prostate biopsy core tissue samples from 498 men from the U.K. and Belgium	Retrospective ConfirmMDx performed on first biopsy	Repeat biopsy	NR	<30 mo	Yes	73% of men had benign DRE; median PSA level was 5.9 ng/mL

DRE: digital rectal exam; NR: not reported; PSA: prostate-specific antigen.

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Table 29. Results of Clinical Validity Studies Assessing ConfirmMDx

Study; Trial	Initial N	Final N	Excluded Samples	Prevalence of Condition	Clinical Validity (95% Confidence Interval), %			
					Sens	Spec	PPV	NPV
Waterhouse et al (2018)	NR	211	NR	81 had positive second biopsy (cases), 130 had negative second biopsy (controls)	74 (63 to 83)	60 (51 to 69)	54 (47 to 60)	79 (72 to 85)
Partin et al (2014); DOCUMENT	350	320	30	92 had positive second biopsy (cases), 228 had negative second biopsy (controls)	62 (51 to 72)	64 (57 to 70)		88 (85 to 91)
Stewart et al (2013); MATLOC	498	483	15	87 had positive second biopsy, 396 had negative second biopsy (controls)	68 (57 to 77)	64 (59 to 69)		90 (87 to 93)
Summary					51 to 83	51 to 70	54	72 to 93

NPV: negative predictive value; NR: not reported; PPV: positive predictive value; Sens: sensitivity; Spec: specificity.

Tables 30 and 31 summarize the relevance and design and conduct gaps in each study.

Table 30. Relevance Gaps

Study; Trial	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-Up ^e
Waterhouse et al (2018)		1. Classification thresholds not described (proprietary)			
Partin et al (2014); DOCUMENT		1. Classification thresholds not described (proprietary)			
Stewart et al (2013); MATLOC		1. Classification thresholds not defined. Training set with a stepwise approach to maximize NPV			

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. NPV: negative predictive value.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

^c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

^d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

^e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

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Table 31. Study Design and Conduct Gaps

Study; Trial	Selection ^a	Blinding ^b	Delivery of Test ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Waterhouse et al (2018)	1. Selection not described				1. Inadequate description of indeterminate and missing samples	
Partin et al (2014); DOCUMENT						
Stewart et al (2013); MATLOC						

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).

^b Blinding key: 1. Not blinded to results of reference or other comparator tests.

^c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

^d Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

^f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Subsection Summary: Clinically Valid

Three retrospective clinical validation studies have reported on the ConfirmMDx score in men who have undergone repeat biopsy. The studies did not provide estimates of validity compared with other risk prediction models. ConfirmMDx was shown to be the most significant predictor of patient outcome in a multivariate model that included age, PSA level, DRE, and first biopsy histopathology characteristics. Sensitivity ranged from 62% to 74% and NPV from 79% to 90%. In a subsequent analysis of ConfirmMDx in men with high-grade prostate cancer on rebiopsy, the NPV was 96%, but the precision of the estimate was not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Aubry et al (2013) estimated the reduction in biopsies associated with ConfirmMDx use. Using the performance characteristics from MATLOC, the authors estimated that 1106 biopsies per 1 million people would be avoided. The study did not include a decision analysis comparing the tradeoff in a reduction in biopsies and missed cancers.

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The Prostate Assay Specific Clinical Utility At Launch (PASCUAL) trial is an observational trial that assessed the impact of the ConfirmMDx test on physician decisions for repeat biopsy. MDxHealth completed enrollment into the PASCUAL trial in April 2015. As of July 2018, the study had been halted pending analysis for termination.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of ConfirmMDx has not been established, a chain of evidence supporting the clinical utility of this test cannot be constructed.

Section Summary: Gene Hypermethylation and ConfirmMDx

No studies were found that directly show the effects of using ConfirmMDx test results on clinical outcomes. Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. The ConfirmMDx test is associated with a diagnosis of prostate cancer and aggressive prostate cancer, but studies did not compare performance characteristics with standard risk prediction models. No data are currently available on the longer term clinical outcomes of the men who did not have biopsy based on ConfirmMDx results. Results of the PASCUAL trial have not been reported. The chain of evidence is incomplete.

Prostate Core Mitomics Test

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Robinson et al (2010) assessed the clinical value of a 3.4-kilobase mitochondrial deletion in predicting rebiopsy outcomes. Levels of the deletion were measured by quantitative polymerase chain reaction in prostate biopsies negative for cancer from 101 men who underwent repeat biopsy within 1 year and had known outcomes. The clinical performance of the deletion was calculated with the use of an empirically established cycle threshold cutoff, the lowest cycle threshold as diagnostic of prostate cancer, and the histopathologic diagnosis on the second biopsy. Final data were based on 94 patients, who on the second biopsy had 20 malignant and 74 benign diagnoses. The cycle cutoff gave a sensitivity and specificity of 84% and 54%, respectively, with an area under the receiving operating curve of 0.75. The NPV was 91%.

Subsection Summary: Clinically Valid

The Prostate Core Mitomics Test (PCMT) has preliminary data on its performance characteristics in a small validation study, showing sensitivity of 84%, specificity of 91%; and NPV of 91%.

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Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Legisi et al (2016) queried a pathology services database to identify (1) men who had a negative initial prostate biopsy and a negative PCMT (n=644), and (2) men who had a negative initial prostate biopsy and a repeat biopsy (n=823). Of the 644 patients with a negative PCMT, 35 had a repeat biopsy and 5 (14.2%) were false-negatives who were found to have cancer on rebiopsy. The number of false-negatives of the patients who did not have a repeat biopsy cannot be determined from this study. Of the second group of 823 men who had a repeat biopsy, 132 had a PCMT. Changes in physician decision-making led to earlier detection of prostate cancer by 2.5 months and an increase in cancer detection rates, but this was only observed when men with atypical small acinar proliferation on index biopsy were not included. Interpretation of these results is limited because testing was not random or consecutive.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of PCMT has not been established, a chain of evidence supporting the clinical utility of this test cannot be constructed.

Section Summary: Prostate Core Mitomics Test

No studies were found that directly show the effects of using PCMT results on clinical outcomes. Given the lack of direct evidence of utility, a chain of evidence would be needed to demonstrate clinical utility. The PCMT has preliminary data on performance characteristics in a small validation study, but independent confirmation of clinical validity is needed. The studies did not provide estimates of validity compared with clinical examination and standard risk scores. Changes in physician decision-making led to earlier detection of prostate cancer and an increase in cancer detection rates, but the interpretation of these results is limited by potential selection bias. No data are available on the long-term clinical outcomes. Data on clinical utility are lacking.

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Candidate Gene Panels

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

A 3-gene panel (*HOXC6*, *TDRD1*, *DLX1*) developed by Leyten et al (2015) is now commercially available as SelectMDx (see above). Xiao et al (2016) reported the development of an 8-gene panel (*PMP22*, *HPN*, *LMTK2*, *FN1*, *EZH2*, *GOLM1*, *PCA3*, *GSTP1*) distinguished high-grade prostate cancer from indolent prostate cancer with a sensitivity of 93% and NPV of 61% (see Tables 32 and 33).⁵⁶ Validation of this panel is needed.

Table 32. Characteristics of Clinical Validity Studies Assessing Candidate Gene Panels

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Xiao et al (2016)	Specimens from 158 men	Retrospective	High-grade prostate cancer on biopsy			

Table 33. Results of Clinical Validity Studies Assessing Candidate Gene Panels

Study	N	Clinical Validity (95% Confidence Interval), %			
		Sensitivity	Specificity	PPV	NPV
Xiao et al (2016); 8-gene panel	158	93 (88 to 97)	70 (36 to 104)	98 (95 to 100)	61 (25 to 97)

AUC: area under the curve; NPV: negative predictive value; PPV: positive predictive value.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of these multigene tests has not been established, a chain of evidence supporting the clinical utility of these tests cannot be constructed.

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Section Summary: Candidate Gene Panels

Numerous studies have demonstrated the association between SNVs and prostate cancer. Gene panels that evaluate the likelihood of prostate cancer on biopsy are in development.

SUMMARY OF EVIDENCE

For individuals who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health Index, TMPRSS fusion genes and Mi-Prostate Score, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifyny, PCA3 score), the evidence includes systematic reviews, meta-analyses, and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The evidence supporting clinical utility varies by test but has not been directly shown for any biomarker test. Absent direct evidence of clinical utility, a chain of evidence might be constructed. However, the performance of biomarker testing for directing biopsy referrals is uncertain. While some studies have shown a reduction or delay in biopsy based on testing, a chain of evidence for clinical utility cannot be constructed due to limitations in clinical validity. Test validation populations have included men with a positive digital rectal exam, a PSA level outside of the gray zone (between 3 or 4 ng/mL and 10 ng/mL), or older men for whom the information from test results are less likely to be informative. Many biomarker tests do not have standardized cutoffs to recommend a biopsy. In addition, comparative studies of the many biomarkers are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test), the evidence includes systematic reviews and meta-analyses and primarily observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, resource utilization, and quality of life. The performance of biomarker testing for guiding rebiopsy decisions is lacking. The tests are associated with a diagnosis of prostate cancer and aggressive prostate cancer, but studies on clinical validity are limited and did not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on physician decisions on rebiopsy or on the longer term clinical outcomes of men who did not have biopsy based on test results. The evidence is insufficient to determine the effects of the technology on health outcomes.

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10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. New policy.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Minor change to coverage statement ("prognosis" added to the investigational statement on PCA3).
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	Coding updated
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Added Kallikrein markers (4Kscore test), metabolomics profiles (Prostarix), candidate gene panels, mitochondrial DNA mutation testing (Prostate Core Mitomics test), and gene hypermethylation testing (ConfirmMDx) to INV statement. Title change.
10/06/2016	Medical Policy Committee review
10/19/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. Added Prostate Health Index (phi) to investigational statement and rationale. Updated rationale and references.
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. Policy revised to separate initial biopsy and repeat biopsy populations, policy statement otherwise unchanged.
10/29/2018	Coding update
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. The SelectMDx, ExoDx Prostate (IntelliScore), and Apify tests added as investigational.

Next Scheduled Review Date: 01/2020

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